REMARKS

Claims 1, 5, 7-10, 14-18, 22, 24-29, 31-35, 37-40, and 42-45 remain in the application.

Favorable reconsideration is respectfully requested.

Rejection of Claims 1, 5, 7-10, 14-18, 22, 24-29, 31-35, 37-40, and 42-45 Under 35 USC §103(a) Over Mizutani et al. (*Microbiol. Immunol.*, Vol 42(8), pp549-553, 1998) and Ambion, Inc., TechNotes 8(2) "SUPERase.In: The Right Choice for Protecting Your RNA," hereinafter "Ambion":

Applicants respectfully traverse this rejection.

Applicants maintain the position that there is no technological reason or motivation to combine the Mizutani et al. and Ambion references. The justification provided by the Examiner for combining the references is the following: "The motivation for the inclusion of SUPERnasin Ribonuclease inhibitor in the methods of RT-PCR taught by Mizutani et al., is that SUPERnasin inhibits **RNases that are known contaminants of RNA preparations**" (see page 6, paragraph 3 of Office Action dated June 3, 2008 and page 10 of Office Action dated December 10, 2007).

However, the combination of references fails to provide any evidence or suggestion that "RNAses...are known contaminants of RNA preparations." Mizutani et al., for example, are silent with respect to RNases or any type of RNase inhibitor. This point has been acknowledged on record by the Office (see page 7, first full paragraph of Office Action dated June 3, 2008). Mizutani et al. are also completely silent with respect to any other means of mitigating effects of RNases in their RNA preparations. Thus, Mizutani et al. does not suggest that RNases are known contaminants of RNA preparations.

The Ambion reference also fails to provide any indication that RNases are known contaminants of RNA preparations. The reference suggests several means by which RNase contamination **"might originate"** (see line 5 of section entitled "Inhibit More RNases Than Any Other Inhibitor), but it does not suggest that RNases are known contaminants of RNA preparations—whether all, the majority, or even some RNA preparations. The Ambion protocol states that the RNase inhibitor described therein "can

be used in any application where RNase contamination is a concern" (see first paragraph). However, the fact that Mizutani et al. employ a protocol for a single-step RT-PCR reaction in the absence of RNase inhibitors is *prima facie* evidence that **RNases are not known contaminants of RNA preparations** and therefore are not a concern in their RT-PCR method. Because neither of the cited prior art references provides any suggestion that RNases are known contaminants of RNA preparations, Applicants submit that the examiner's justification for combining the references is improper.

The Office has stated that in the case of heating a mixture containing an RNase inhibitor to 90 °C in the RT-PCR method of Mizutani et al. **after** reverse transcription of RNA, where the RNA is no longer needed, the RNase inhibitor would still be present and Applicants' claims would therefore be obvious. However, Applicants submit, first, that for the inhibitor to be present, there needs to be motivation to include it in the RT-PCR reaction in the first place, a motivation that the Office has failed to establish. Second, Applicants submit that if the inhibitor were to be present, Applicants' claims would still not be obvious because all the claimed elements would still not be met. For example, Claim 1 of the present application clearly requires the following elements relating to heating the mixture:

(1) that the mixture be heated to **no less than about 90 °C**;
(2) that the mixture is heated **for a time sufficient to inhibit RNase activity** present in the mixture; and
(3) whereby RNA is **protected from enzymatic degradation by RNases.**

The combination of the Mizutani et al. and Ambion references fails to suggest all the required elements. On one hand, Mizutani et al. may heat their mixture to no less than about 90 °C, but they do not test for—or even suggest to test for—any inhibition of RNase activity or protection from RNase degradation after heating. Additionally, they do not provide any assay to test for RNase activity. Successful amplification of DNA in the method of Mizutani et al. provides no such method to determine RNA protection because the RNA is reverse-transcribed before heating to 90 °C, and the stability (or instability) of RNA has no effect on DNA amplification after the RNA has been reverse-transcribed.

On the other hand, the Ambion reference may test for inhibition of RNase activity or protection from RNase degradation, but there is no indication that such activity would occur at temperatures anywhere approaching 90 °C because 90 °C is far outside of the stated effective temperature range of the Ambion inhibitor: 4 °C to 65 °C (see section entitled "SUPERase.In Is Active Over a Broader Range of Conditions Than RI").

Finally, the Ambion reference, like Mizutani et al., does not provide an assay suitable for determining if heating the RNase inhibitor to 90 °C in the method of Mizutani et al. successfully inhibits RNA degradation. The assays for detecting RNase activity in the Ambion reference include a microplate assay and a denaturing PAGE assay of radiolabeled, RNase inhibitor-treated RNA probes. These assays provide no guidance for determining RNA protection in the RT-PCR method of Mizutani et al. It is completely unclear how one would combine either the microplate assay or denaturing PAGE assay of Ambion with the RT-PCR assay of Mizutani et al. because they are directed to completely different biochemical outcomes.

In short, the combination of references does not in any way suggest that heating the RNase inhibitor of Ambion at 90 °C for any given time period would successfully inhibit RNase activity; nor does it suggest a way of determining if inhibition would occur. Because the required elements of Claim 1, for example, are not met, Applicants submit that the combination fails to render obvious Applicants' claims.

Applicants maintain that there is also no motivation to combine the Mizutani et al. and Ambion references because the Ambion reference teaches away from using the RNase inhibitor in the method of Mizutani et al. Applicants have asserted that the Ambion reference clearly teaches in Figure 2 and elsewhere that heating RNase inhibitors releases latent RNase activity present in the inhibitors. In response, the Office has asserted on record that "at the point of the...method at which the temperature is raised to 90 °C, the RNase inhibitor is no longer necessary" (see page 7, second full paragraph of Office Action dated July 3, 2008). Applicants agree with this statement by the Office. However, this fact only indicates that heating the RNase of Ambion in the method of Mizutani et al. is not only discouraged by Ambion but is also unnecessary. In short, it follows from the assertion by the Office that there would be no motivation to combine the references to arrive at the claimed method because there would be no utility in doing so.

Applicants therefore submit that this rejection is improper. Withdrawal of the same is respectfully requested.

CONCLUSION

Applicants submit that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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